Radiographic Emphysema Predicts Osteopenia, Osteoporosis in Smokers

Radiographic Emphysema Predicts Low Bone Mineral Density in a Tobacco Exposed Cohort.

Bon J, Fuhrman CR, et al:
Am J Respir Crit Care Med 2010; (October 8): epub ahead of print

In this study, the severity of radiographic emphysema is the strongest independent predictor of bone loss in a cohort of smokers with generally mild airflow obstruction.

Background: Epidemiologic studies have demonstrated an association between COPD and low bone mineral density (BMD). The specific mechanisms responsible for this relationship have not been determined. Radiographic emphysema has been reported to be an independent predictor of several systemic manifestations of COPD, including vascular stiffness and lung cancer risk.

Objective: To explore associations of BMD with radiographic measures of emphysema and other risk factors in a group of current and ex-smokers.

Design/Participants: Cross-sectional, observational study involving 190 subjects participating in the COPD Specialized Center for Clinically Oriented Research at the University of Pittsburgh.

Methods: The mean smoking history was 54 pack years. The average FEV₁ was 80.7% with GOLD staging: 38.4% at risk; 18.4% stage I; 33.2% stage II; 10% stage III; and 0% stage IV; 17.9% were on inhaled corticosteroids and 4.7% were on systemic steroids. Demographic and physical activity questionnaires, chest CT, spirometry, DLCO, and dual x-ray absorptiometry (DXA) measurements of BMD at the hip and spine were performed on each subject. Emphysema was quantified using both a semiquantitative visual scoring system and by the percentage of low attenuation units. Osteopenia was defined as a BMD >1 but <2.5 standard deviations below the reference mean at either site. Osteoporosis was defined as a BMD >2.5 standard deviations below the reference mean.

Results: 36.3% had no emphysema, 44.7% had trace-to-mild emphysema, and 19.0% had moderate-to-severe emphysema; 33.2% had normal BMD, 57.9% had osteopenia, and 8.9% had osteoporosis. Using a multivariate logistic regression analysis to correct for the various risk factors associated with low BMD, the presence and severity of radiographic emphysema was the strongest independent predictor of osteopenia/osteoporosis (OR, 3.68 for moderate-to-severe emphysema and 2.33 for trace-to-mild emphysema). Female gender was also an independent risk factor. Physical activity, steroid use, and airflow obstruction were not independent predictors of a low BMD.

Conclusions: Radiographic emphysema is an independent predictor of low BMD in this population of current and former smokers.

Reviewer's Comments: This paper suggests that similar underlying mechanisms might explain both the loss of lung tissue and loss of bone in patients with COPD. There is an increasing body of knowledge supporting COPD as a systemic inflammatory disease. A better understanding of the inflammatory mediators involved may lead to new treatments for both COPD and related comorbidities. Limitations of the study include a relatively small sample size, mild airflow obstruction, limited steroid use, and cross-sectional study design. (Reviewer-Jeff Wilson, MD).

Keywords: Airflow Obstruction, Smoking, Osteopenia, Osteoporosis, Emphysema

Print Tag: Refer to original journal article
Can Inhaled Corticosteroids Reduce Risk of Atherosclerosis?

Reduced Carotid Atherosclerosis in Asthmatic Patients Treated With Inhaled Corticosteroids.

Otsuki M, Miyatake A, et al:

Eur Respir J 2010; 36 (September 1): 503-508

Carotid atherosclerosis appears to be decreased in asthmatic patients treated with inhaled corticosteroids.

**Background:** Inhaled corticosteroids are the mainstay of treatment for all patients with persistent asthma. Inhaled corticosteroids are felt to work by decreasing airway inflammation. Inflammation is known to play a role in the pathogenesis of atherosclerosis.

**Objective:** To compare carotid atherosclerosis in asthmatic patients taking inhaled corticosteroids to a control group of non-asthmatics.

**Design:** Prospective controlled trial.

**Participants/Methods:** Measuring the thickness of the carotid artery intima and media can be used to detect atherosclerosis in carotid arteries. The thickness of the carotid artery intima and media has been shown to be a risk factor for myocardial infarction and stroke. Otsuki and colleagues examined the carotid arteries by ultrasound to look for evidence of atherosclerosis in 150 asthmatics who had regularly been treated with inhaled corticosteroids. They compared them to 150 matched non-asthmatic controls. Carotid atherosclerosis was defined as mean intima and media thickness >1.1 mm and/or the presence of a plaque lesion. A plaque lesion was defined as a distinct area with an intima and media thickness 50% greater than neighboring sites.

**Results:** There were no significant differences in age, sex, body mass index, and the prevalence of hypertension, hyperlipidemia, or diabetes between the 2 groups. Interestingly, the prevalence of smoking status was significantly higher in the asthmatic patients than in the control group. These investigators found that the carotid intima-media thickness was significantly lower in the asthmatic patients than in the control group. The prevalence of carotid plaques tended to be lower in the asthmatic group compared to the control group. The mean daily dose of inhaled corticosteroids was significantly lower in patients with carotid atherosclerosis. There was no significant difference between patients with and without atherosclerosis in relation to those patients treated with β2-agonists, disodium cromoglycate, theophylline, and leukotriene receptor antagonists.

**Conclusions:** Carotid atherosclerosis is reduced in asthmatic patients utilizing inhaled corticosteroids when compared to non-asthmatic matched controls.

**Reviewer’s Comments:** My initial reaction to this article was one of disbelief. Yet when one examines the situation more closely, perhaps a beneficial effect may not be so far-fetched. Daily use of inhaled corticosteroids for 3 weeks has been shown to restore endothelial function in smokers and improve endothelial function in COPD. In the European Respiratory Society study on chronic obstructive lung disease (acronym EUROSCOP), 3-year treatment with budesonide was associated with a 45% reduction in ischemic cardiac events compared to placebo. I do not think anyone today would suggest prescribing inhaled corticosteroids to prevent atherosclerosis. Studies are needed to evaluate and explore the possible relationship between inhaled corticosteroids and atherosclerosis. (Reviewer-Richard A. Nusser, MD).

**Keywords:** Asthma, Carotid Atherosclerosis, Inhaled Corticosteroids

**Print Tag:** Refer to original journal article
Nontuberculous Mycobacterial Disease Is on the Rise

*Pulmonary Nontuberculous Mycobacterial Disease Prevalence and Clinical Features: An Emerging Public Health Disease.*

Winthrop KL, McNelley E, et al:

*Am J Respir Crit Care Med* 2010; 182 (October): 977-982

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Pulmonary infections due to nontuberculous mycobacterial organisms are becoming more common.

**Background:** The epidemiology and prevalence of nontuberculous mycobacterial disease has not been well studied.

**Objective:** Winthrop and colleagues from Oregon Health and Science University sought to evaluate the frequency and clinical characteristics of nontuberculous mycobacterial infection in their area.

**Design:** Retrospective study.

**Methods:** These investigators performed a statewide laboratory based surveillance study for nontuberculous mycobacteria in Oregon. They recorded demographic data and microbiologic information on every Oregon resident who had had nontuberculous mycobacteria isolated during the years 2005 and 2006. They next chose a subset of these patients so they could more easily examine their clinical records. These patients resided in the Portland Tri-County area. For each patient, the investigators reviewed electronic records of clinical features, microbiologic data, and radiographic findings for the 2-year period.

**Results:** 807 Oregonians had nontuberculous mycobacteria isolated in the 2005 and 2006 time period. Of these, 407 (50%) lived in the Portland Tri-County area. A total of 134 of the patients whose full records were available for review met American Thoracic Society/Infectious Disease Society of America guidelines for diagnosis of nontuberculous mycobacteria infection of the lungs. For patients who met criteria for disease, the median age was 66 years; 59% of the patients were female, and approximately 25% had cavitary lung disease. There was evidence of pleural effusions in 17%. Comorbid conditions frequently present in these patients included COPD, lung cancer, and bronchiectasis. Twenty-five percent of the patients were taking either systemic or inhaled corticosteroids when the nontuberculous mycobacteria were isolated. These investigators calculated the prevalence of nontuberculous mycobacterial disease for the 2-year period in the Portland area to be 8.6 cases/100,000 persons. For people aged >50 years, the prevalence was 20.4 cases/100,000 persons. During the same time frame, the annual incidence of mycobacterial tuberculosis infection in the Portland area was 2.5 cases/100,000 persons.

**Conclusions:** Pulmonary disease due to nontuberculous mycobacteria is not uncommon. In the Portland area, it was several-fold more common than mycobacterium tuberculosis infection.

**Reviewer's Comments:** This was a well-done study. I suspect it confirms what many pulmonary physicians have thought – that they are seeing more cases of nontuberculous mycobacterial disease. For patients >50 years of age, nontuberculous mycobacterial infections were 3 times more common than mycobacterium tuberculosis. I was surprised that pleural effusions were seen in 17% of cases. If one references Hansell's, *Imaging of Diseases of the Chest*, pleural effusions are thought to be uncommon with nontuberculous mycobacterial infection. (Reviewer-Richard A. Nusser, MD).

Keywords: Nontuberculous Mycobacterial Disease, Prevalence

Print Tag: Refer to original journal article
Consider Only PA Radiograph for a Positive PPD

Tuberculosis: Value of Lateral Chest Radiography in Pre-Employment Screening of Patients With Positive Purified Protein Derivative Skin Test Results.

Eisenberg RL, Romero J, et al:

Radiology 2009; 252 (September): 882-887

There is no need for a lateral chest radiograph in patients with a positive purified protein derivative.

**Background:** The Centers for Disease Control and Prevention and the American Thoracic Society recommendation for patients with a positive purified protein derivative (PPD) skin test calls for a posteroanterior (PA) radiograph, adding that additional radiographs be obtained at the physician’s discretion. Throughput efficiency makes it impractical to review each patient’s PA radiograph for the potential need for a lateral, resulting in a lateral radiograph being obtained for many patients with a positive PPD.

**Objective:** If only a single PA is adequate for the evaluation for active TB, costs and radiation dose could be decreased and throughput increased.

**Design:** Retrospective institutional review board approved and Health Insurance Portability and Accountability Act compliant study.

**Participants:** Included were 875 adults evaluated in the employee health department of a tertiary care facility. All underwent chest radiography because of a positive PPD skin test result obtained during pre-employment examinations. PA and lateral radiographs were routinely obtained for these patients. Excluded were those Employees who were pregnant or <18 years of age received PA radiographs only and were excluded from the study.

**Methods:** 2 attending chest radiologists independently assessed the radiographs for evidence of chronic or acute tuberculosis (TB). Initially, only the PA radiographs were reviewed. Then, PA and lateral radiographs were reviewed together, noting whether any finding was seen only on the lateral radiograph or was visible on both projections. Discrepancies were resolved by a third reading session. The analysis included how often the lateral image revealed an abnormality that was not apparent on the PA radiograph or changed the interpretation of any abnormality seen on the PA radiograph.

**Results:** 91 of 875 subjects had abnormalities associated with TB, such as a calcified node or granuloma, apical pleural thickening, a noncalcified nodule, or fibrous scarring; no subject had findings of active TB. Of these 91 subjects, the lateral radiograph showed no abnormality in 75. All abnormalities seen on lateral views were also observed on the PA view. In no case did the findings on the lateral view alter the interpretation of the PA radiograph.

**Conclusions:** It is not necessary to obtain the lateral radiograph for this indication. This could result in decreased radiation dose, decreased cost, and increased throughput. However, the study is limited as it was restricted to an asymptomatic pre-employment population with a low incidence of TB disease, creating a selection bias. It was also biased in that the readers only focused on TB-related findings.

**Reviewer’s Comments:** Radiation exposure from diagnostic examinations has become a “hot topic” in today’s radiology community, making this article still timely. Decreasing costs and radiation exposure are important in screening examinations, and the elimination of the lateral radiograph helps accomplish this. However, one must keep in mind that the conclusion of this study is limited to the screening of asymptomatic individuals in a low-risk population pool. (Reviewer–Steven Montner, MD).

**Keywords:** Tuberculosis, PPD, Lateral Radiographs
Indacaterol Is Safe, Effective Alternative to Tiotropium

Once-Daily Bronchodilators for Chronic Obstructive Pulmonary Disease: Indacaterol Versus Tiotropium.

Donohue JF, Fogarty C, et al:

Am J Respir Crit Care Med 2010; 182 (2): 155-162

Indacaterol, a once-daily long-acting β2-agonist, appears to be an effective alternative to tiotropium for maintenance therapy in moderate-to-severe chronic obstructive pulmonary disease.

Background: Long-acting inhaled bronchodilators are recommended for patients with moderate-to-severe COPD. They provide superior bronchodilation and clinical outcomes and enhance compliance compared with short-acting agents. Currently, long-acting β2-agonists are given twice daily. Indacaterol is the first once daily inhaled β2-agonist.

Objective: To evaluate the efficacy of indacaterol in comparison with placebo and tiotropium and to assess the safety and tolerability of indacaterol.

Design/Participants: Randomized, controlled, intention-to-treat trial involving patients with moderate-to-severe COPD.

Methods: After a run-in period to determine the optimal indacaterol dose, patients were divided into 4 arms to receive either placebo, tiotropium, or indacaterol (150 µg or 300 µg) once daily, for 26 weeks. Indacaterol administration was double-blinded, but tiotropium was given open-label. Patients were continued on inhaled steroids and rescue albuterol. The primary outcome measure was the trough FEV1 24 hours after drug inhalation at 12 weeks. Quality-of-life measures and COPD exacerbations were analyzed, but were not adjusted for multiplicity. The study was funded by Novartis Pharmaceuticals.

Results: 1683 patients were randomized to the 4 treatment arms and 77% completed the study. At week 12, compared with placebo, there was a 180 mL increase in trough FEV1 in patients taking indacaterol at both doses and a 140 mL increase for patients taking tiotropium (P <0.001 for all treatments) versus placebo. Similar increases were seen at week 26. The rate of exacerbations was reduced in all 3 treatment groups but generally did not reach statistical significance. Quality-of-life measures improved in all treatment groups (more with indacaterol compared with tiotropium), but did not reach usual criteria for a minimal clinically important difference. There was no difference in the incidence of low serum potassium, high blood glucose, and prolonged QTc.

Conclusions: Indacaterol is a once-daily β2-agonist with efficacy similar to tiotropium.

Reviewer’s Comments: Patients with COPD benefit from therapy with long-acting bronchodilators. Tiotropium is the only once-daily bronchodilator currently available in the United States. The authors of this well-designed study provide data that indacaterol is an effective and safe alternative to tiotropium. The onset of bronchodilation with indacaterol is fast, occurring within 5 minutes of inhalation. Cough was more frequent during inhalation of indacaterol but did not lead to increased patient drop-out. Indacaterol appears to be a useful addition to the pharmacological management of moderate-to-severe COPD. Longer trials will be needed to confirm whether it reduces frequency of exacerbations, as tiotropium has been shown to do. It will also be interesting to see whether the combination of tiotropium and indacaterol are superior to either drug alone. (Reviewer-Jeff Wilson, MD).

Keywords: Long-Acting Bronchodilators, Indacaterol, Tiotropium

Print Tag: Refer to original journal article
Background: Ambulatory oxygen is frequently prescribed for dyspneic patients with COPD who do not have resting hypoxemia, but may have oxygen desaturation with exertion. The benefit of supplemental oxygen in this setting is unclear.

Objective: To determine whether patients with COPD without resting hypoxemia benefit from using supplemental oxygen with ambulation.

Design: A 12-week, parallel, double-blinded, randomized, placebo-controlled trial with intention-to-treat analyses.

Methods: 143 subjects with moderate-to-severe COPD (mean FEV₁, 1.16 L and resting PaO₂ ≥55) were randomized to use either cylinder air or cylinder oxygen at 6 L/min flow for any activity causing dyspnea. Thirty-five percent of participants demonstrated exertional oxygen desaturation (SpO₂ ≤88%). The primary outcome measure was dyspnea and health-related quality of life (QOL) measured by the Chronic Respiratory Disease Questionnaire (CRDQ). Secondary outcomes included other QOL measures, 6-minute walk distance (6MWD), activity (assessed by patient diary and pedometer count), and gas cylinder use.

Results: The 2 groups were well matched after randomization, and 97% completed the study. Small improvements in dyspnea (CRDQ) were seen in both groups at 12 weeks, but they did not reach standard criteria for a clinically meaningful minimal important difference (MID). No significant differences in other QOL measures were seen. 6MWD for the entire group increased 10.7 meters breathing cylinder oxygen compared to breathing cylinder air. In the subgroup of patients with exertional oxygen desaturation, the 6MWD increased 13.8 meters wearing oxygen compared with air. These changes were not close to the usual MID for the 6MWD of 54 meters. No significant differences were seen in the other functional activity measures or in the number of cylinders used by each group. Further analysis of 6 variables (exertional desaturation, severity of airflow obstruction, gender, severity of dyspnea, and change in inspiratory capacity or 6MWD with oxygen) failed to find a subgroup predictive of reduced dyspnea with oxygen.

Conclusions: In this 12-week trial, ambulatory oxygen conferred no significant benefit in a group of patients with moderate-to-severe COPD without resting hypoxemia.

Reviewer’s Comments: Prescribing supplemental oxygen for patients with COPD who do not have hypoxemia at rest, but desaturate with exertion, is common practice. Improvement in exercise tolerance in this patient population has been shown with supplemental oxygen in the laboratory setting. However, several clinical trials in "real life" settings have not shown significant benefits. It is not uncommon in my practice for patients prescribed oxygen for use only with exertion to return indicating they do not feel it has helped them. I think it is likely that the energy cost to the patient of transporting the cylinders (even the smallest ones) outweighs the potential benefits of higher oxygen saturation. (Reviewer-Jeff Wilson, MD).

Keywords: Oxygen, Dyspnea, Quality of Life

Print Tag: Refer to original journal article
Variability of N1 Resection May Affect Outcome of Early Stage NSCLC

Variability in Defining T1N0 Non-Small Cell Lung Cancer Impacts Locoregional Failure and Survival.
Saynak M, Hubbs J, et al:

The lack of precise N1 staging may impact the outcome of early stage non-small-cell lung cancer.

**Background:** Lung cancer is associated with a poor prognosis. Even at early stages, patients often develop locoregional recurrent disease. This may in part be due to inadequate nodal staging or incomplete resections. Nodal involvement is predictive of outcome in patients with non-small-cell lung cancer (NSCLC) and dictates if further treatment is warranted.

**Design/Participants:** Retrospective analysis of 742 patients previously untreated (no chemotherapy or radiation) who underwent lobectomy/pneumonectomy between 1996 and 2006.

**Methods:** The medical records, including operative and pathology reports, were reviewed. The number of lymph nodes and nodal stations were evaluated, and recurrence rates and disease-free survival were calculated and compared based on operative and pathologic lymph node status.

**Results:** The study identified 119 patients with pathological T1N0 NSCLC. Mediastinal lymph nodes (N2) were dissected and evaluated in 94% of patients. Median lymph node N2 stations examined were 2. Patients were classified to have defined N1 lymph nodes examined if there was adequate mapping of lymph nodes and undefined if N1 lymph nodes were not mapped and deemed "peribronchial." Both groups did have N1 nodes evaluated. Median N1 lymph nodes examined was 5, and 70% of patients had ≥1 defined N1 station, 27% had undefined, and 3% had no N1 lymph nodes examined. Locoregional recurrence was 14% with defined and 31% with undefined N1 dissection (P =0.03). Disease-free survival trended toward improvement, with 78% in defined and 63% in undefined N1 dissection (P =0.06).

**Conclusions:** There is a high rate of locoregional recurrence and a trend toward decreased survival in patients who have undefined N1 dissections. Despite adequate resection and N2 analysis, a lack of precise N1 mapping may contribute to downstaging and inadequate treatment of early stage lung cancer.

**Reviewer's Comments:** This is a provocative retrospective study that shows a trend toward worsened outcomes if lymph node staging is not done precisely. It is unclear if patients who had defined lymph node dissections had a larger more comprehensive resection, hence, a decreasing likelihood of downstaging. Nonetheless, this is an important factor in determining which patients should get further treatment. I would encourage all pulmonologists who refer NSCLC patients to thoracic surgery to demand thorough and well-defined lymph node dissections to aid in decisions regarding adjuvant therapy for this disease. Adequate lymph node dissections should include systematic approaches including multiple lymph nodes from multiple stations with locations described. These dissections depend on the site of the tumor. (Reviewer-Victoria M. Villaflor, MD).

Keywords: Lung Cancer, Resection, Nodal Staging

Print Tag: Refer to original journal article
Endosonography added to surgical staging of lymph nodes has superior sensitivity compared to surgical staging alone in this study.

**Background/Objective:** Surgical staging by mediastinoscopy is considered standard practice prior to surgical resection in patients with resectable non-small-cell lung cancer (NSCLC). Mediastinoscopy has limitations. Minimally invasive endosonography has been shown to be able to evaluate lymph nodes in the mediastinum and, hence, is studied here for an alternative to immediate surgical staging.

**Methods:** Patients were randomized to either have mediastinoscopy or endosonography (combined transesophageal and endobronchial ultrasound [EUS-FNA and EBUS-TBNA]) with subsequent mediastinoscopy if no nodes were found with EUS-FNA/EBUS-TBNA. Thoracotomy with lymph node dissection was performed in patients who did not have evidence of mediastinal disease. Primary outcome was sensitivity of mediastinal lymph node metastasis N2/N3 compared to surgical pathological staging.

**Results:** 241 patients were randomized, 123 to endosonography (65 of whom also had mediastinoscopy) and 118 to mediastinoscopy. Mediastinal disease (N2/N3) was found in 41 patients (35%) having only mediastinoscopy versus 56 patients (46%) with endosonography alone ($P=0.11$) versus 62 patients (50%) who had both endosonography and mediastinoscopy ($P=0.02$). Sensitivity of mediastinoscopy alone was 79% versus 85% for endosonography alone and 94% for both endosonography and mediastinoscopy ($P=0.02$). This resulted in 21 unnecessary thoracotomies in the mediastinoscopy group and 9 in the endosonography group ($P=0.02$). Complications were similar in both groups.

**Conclusions:** Endosonography, when combined with mediastinoscopy, improved sensitivity for detecting mediastinal node metastasis and resulted in fewer unnecessary thoracotomies.

**Reviewer's Comments:** This is an interesting and provocative study evaluating the utility of endosonography in the staging of mediastinal lymph nodes to reduce the rate of unnecessary thoracotomies. Thoracotomies can result in increased morbidity and mortality for patients, especially those who have multiple comorbidities as lung cancer patients often do. It is difficult to adequately stage patients prior to surgery. Mediastinoscopy has long been the standard of care for mediastinal lymph node staging. As demonstrated in this study, sensitivity is slightly decreased in patients who have had mediastinoscopy only. This may result in inadequate treatment as concurrent chemoradiotherapy may be indicated in patients who have N2 or N3 disease. Following a thoracotomy, combined chemoradiotherapy would be difficult. Additionally, patients with bulky N2 or N3 disease are not surgical candidates; therefore, having an increase in sensitivity of detecting lymph node metastasis may reduce morbidity and mortality risks of surgery. Often, patients with N2 disease may benefit from down staging their tumor prior to resection. This remains somewhat controversial. The issues that remain with this technology are as follows: (1) Are endoscopic ultrasound and bronchoscopic ultrasound adequate to replace mediastinoscopy as some staging recommendations have suggested? (2) Is this ready for prime time in low volume centers? (Reviewer-Victoria M. Villaflor, MD).

**Keywords:** Lung Cancer, Lymph Node Staging

**Print Tag:** Refer to original journal article
Prone expiration CT imaging can enhance the detection of air trapping.

**Background:** The detection of air trapping on expiration CT is essential for the detection of small airways disease and is important in making the diagnosis of bronchiolitis obliterans, which can complicate lung transplantation. Expiration air trapping shows a gravitational gradient in normal individuals, with the distribution reversing on prone imaging.

**Objective:** To determine whether there is an increased gravitational gradient effect on air trapping in diseased individuals, and whether combining prone expiration imaging with standard supine expiration imaging would aid in the detection of small airways disease.

**Design:** University ethics committee-approved protocol with written informed consent.

**Participants:** This study involved 49 consecutive patients after double-lung transplant (n=30) and combined heart-lung transplant (n=19) during annual CT follow-up. Two patients were excluded due to breathing artifacts on the CT images.

**Methods:** Pulmonary function tests were used to diagnose and grade the severity of bronchiolitis obliterans syndrome (BOS). Patients were grouped as follows: clinically silent bronchiolitis, potential bronchiolitis, and clinically overt bronchiolitis. Non-contrast-enhanced CT scans were performed in full inspiration and expiration and with the patients in the supine and prone positions, with a slice thickness of 1.25 mm. Using full suspended inspiration images for comparison, expiration sections were analyzed for air trapping using the entire section, then separately for the dependent and nondependent regions on both supine and prone series. The average extent of air trapping was calculated for supine and prone images, as well as the percentage of air trapping by combining a segmented analysis of the dependent and non-dependent regions of the lung.

**Results:** For patients in all 3 groups, there was no significant change in the average extent of air trapping in the supine and prone positions. However, there was a statistically significant increase in air trapping in the analysis of the combined dependent lung regions.

**Conclusions:** Air trapping is the result of early closure of small airways, whether these airways are normal or diseased with a reduced caliber. Adjacent pulmonary lobules may have different volumes at end expiration, resulting in different CT attenuation. The increased weight of the lung in its dependent portions reduces the elastic traction exerted on the small airways, promoting small airway closure and making air trapping more visible in these regions. Using a combined method of reading the dependent and independent lung regions in the supine and prone positions, there was a statistically significant increase in the extent of air trapping, but it may not be worth the trade off of increased radiation dose to the patient.

**Reviewer's Comments:** The article is well thought out and helps explain some of the physiology of air trapping. Although a statistically significant difference in the extent of air trapping was revealed using a method of combing readings, this may not outweigh the trade off of increased radiation dosage. (Reviewer-Steven Montner, MD).

**Keywords:** Air Trapping, Expiratory CT, Physiology, Small Airways Disease, Bronchiolitis

**Print Tag:** Refer to original journal article
The use of compression stockings alone in stroke patients who are immobile may not be as beneficial as was shown in prior meta-analyses that largely included surgical patients.

**Background:** In the first CLOTS (Clots in Legs Or sTOckings after Stroke) trial, thigh-length stockings were compared to no stockings in immobile, stroke patients with no statistical difference in deep venous thrombosis (DVT).

**Objective:** To compare below-the-knee stockings with thigh-length stockings in their effectiveness for DVT prophylaxis in the same patients.

**Design:** Multicenter, multinational, randomized, parallel-arm study.

**Methods:** Patients who were immobile after stroke were eligible for enrollment. Patients were randomized to either of the stocking lengths, and 2 lower-extremity compression ultrasound studies (LCUS) were performed. The first study was done on the majority of patients between study days 7 and 10. Nearly all second studies were performed at around day 30. The primary end points were symptomatic or asymptomatic proximal DVTs on either planned LCUS or identification of proximal DVT as a consequence of symptoms in the first month after enrollment.

**Results:** Despite the apparent non-benefit of thigh-length stockings compared to no stockings in the first CLOTS trial, there was a significant reduction in this primary end point in those wearing the longer stockings versus calf-length stockings in this study. Local skin problems were reported more commonly with the longer stockings, but there was no difference in the rate of severe complications (ie, ischemia or amputation).

**Conclusions:** Thigh-length stockings appear to be the better choice over below-the-knee stockings for DVT prophylaxis in patients immobilized after stroke. When these results are considered along with those of the first CLOTS trial, there is a suggestion that the shorter stockings may be causing more proximal DVTs. One explanation is that below-the-knee clots do not improve venous flow properties in more proximal veins that are prone to stasis when immobilized after a stroke. This seems counter to the intuition that most proximal clots propagate from below-the-knee locations. An alternate hypothesis offered by the investigators is that there must have been a type II (or beta) error in the CLOTS-1 trial, and the magnitude of benefit of longer stockings over no stockings was underestimated. If this were true, then perhaps no difference exists between shorter stockings or longer stockings, thereby removing the causal blame from the former.

**Reviewer's Comments:** These results are thought provoking and require further investigation into the potential harm of below-the-knee stockings. Our practice after stroke coincides with consensus recommendations to use heparin in patients who do not disqualify based on risks. Due to the suggestion of no benefit and even harm with different length stockings over no stockings and the magnitude of DVT/pulmonary embolism in this population, it seems reasonable that these guidelines should be followed after stroke. For those who cannot tolerate heparin therapy, CLOTS-3 may eventually offer some guidance with the role of sequential compression devices. (Reviewer-Ajeet G. Vinayak, MD).

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**Keywords:** Compression Stockings, Deep Vein Thrombosis, Stroke

**Print Tag:** Refer to original journal article
**Objective:** To study the safety and satisfaction of patient-controlled sedation (PCS) in mechanically ventilated patients.

**Participants/Methods:** 17 patients who were mechanically ventilated, had stable or improving pulmonary status, and who had received intravenous sedation within the past 24 hours were selected to participate. All patients were alert, able to understand simple English commands, and were able to grip and press the PCS button. Exclusion criteria included planned surgery or extubation within the next 24 hours, vasopressor use, systolic blood pressure (BP) <95 mm Hg for >2 hours in the past 24 hours, current dexmedetomidine use, liver or renal failure, bradycardia (<60 bpm), history of heart block, heart transplant, systolic heart failure, allergy to dexmedetomidine, or pregnancy. Also excluded were patients receiving sedation for non-mechanical ventilation reasons. PCS was tested for up to 24 hours by patient demand bolus and the infusion pump system. The method of calculating the dosage delivered is clearly described, and the reason for choosing dexmedetomidine is discussed. Nurses adjusted infusion rates, and 3 boluses were allowed per hour. If the patient was using a sedative infusion at the time of enrollment, that medication was tapered over 24 hours. Scheduled sedatives and analgesics were changed as needed. Adverse events were considered as follows: heart rate <55 bpm for >5 minutes, systolic BP <90 mm Hg, diastolic BP <55 mm Hg, and mean arterial pressure <60 mm Hg on 2 measurements 10 minutes apart.

**Results:** Of the 17 patients enrolled, 8 were men. The mean age was 47.1 years, and time on the ventilator ranged from 2 to 63 days. Patient diagnoses are listed in the article, and infusion rates and the number of bolus doses are also reported. Subjects were removed from the study due to adverse reactions. Five subjects were extubated after 24 hours. One subject was withdrawn due to unexpected surgery, and one was withdrawn due to "feeling funny." The subjects and nurses rated the sedation as adequate 77% to 100% of the time. Patient and nurse satisfaction with the protocol and medication effect was very positive.

**Conclusions:** This pilot study allows properly selected patients to control sedation while on mechanical ventilation. It appears to be safe and offers another method of extubation, but more study is needed.

**Reviewer's Comments:** This is a very nice study. It points out that patients may be better at determining their level of needed sedation than nurses or physicians. Proper patient selection is vital before this type of protocol can be used. Earlier extubation, less ICU time, and lower costs may result. (Reviewer-Allan R. Goldstein, MD).

Keywords: Sedation, Mechanical Ventilation

Print Tag: Refer to original journal article
The onset of bronchiolitis obliterans syndrome (BOS) within 2 years after transplantation or grade 2 or 3 BOS is associated with worse survival after lung transplantation.

**Background:** Development of bronchiolitis obliterans syndrome (BOS) has been associated with worse survival after lung transplantation. However, little is known regarding the factors that influence survival after the onset of BOS in bilateral lung transplant recipients.

**Objective:** To identify factors that influence survival after the development of BOS among bilateral lung transplant recipients.

**Design:** Prospective, observational cohort study.

**Methods:** The authors assessed the effect of clinical and demographic variables on the development of BOS in 95 bilateral lung transplant recipients using Cox proportional hazards methods.

**Participants:** 95 bilateral lung transplant recipients who developed BOS were compared to 222 lung recipients who had not yet developed BOS.

**Results:** Early onset BOS (within 2 years) was associated with increased mortality (HR, 10.15 per year; 95% CI, 6.15 to 16.75; P<0.0001). At mean follow-up of 5.8 years, 51% of those with BOS had died compared to 22% of those without BOS. In addition, high-grade BOS (grade 2 or 3) was associated with increased mortality compared to grade 1 BOS (HR, 2.40; 95% CI, 1.34 to 4.32; P<0.0034). Clinical variables including baseline demographics, acute rejection, cytomegalovirus infection, or rejection treatment were not associated with survival after BOS development. The effect of both early onset and high-grade onset persisted in multivariate analysis.

**Conclusions:** BOS is a heterogeneous syndrome that is associated with different outcomes after lung transplantation. A better definition of the patterns of BOS will improve our ability to design future studies and assess response to therapies in lung transplantation.

**Reviewer's Comments:** This study highlights an important issue in lung transplantation--namely, that BOS has several different phenotypes that are associated with variable outcome after lung transplantation. This study is rigorously conducted and appropriately analyzed. The data presented will assist in stratifying lung recipients in the future to determine the benefits of potential therapies to improve survival after lung transplantation. (Reviewer-Sangeeta M. Bhorade, MD).

Keywords: Bronchiolitis Obliterans Syndrome, Lung Transplantation

Print Tag: Refer to original journal article
How Many Tidal Breaths Are Necessary via Valved Holding Chambers in Young Asthmatics?

Aerosol Inhalation From Spacers and Valved Holding Chambers Requires Few Tidal Breaths for Children.

Schultz A, Le Souëf TJ, et al:

Pediatrics 2010; 126 (December): e1493-e1498

Young asthmatic children appear to breathe deeper than we expect when using valved holding chambers, and 2 to 3 tidal breaths may be enough to provide adequate drug delivery.

**Background:** A spacer/valved holding chamber (VHC) aids in the delivery and thus efficacy of inhaled medications in children with asthma. In general, young (preschool) children are not able to take a large maximal inhalation as is recommended for older children using a spacer/VHC. Usually, preschool children are instructed to breath tidally through the spacer/VHC. However, no data are available on the appropriate number of tidal breaths to ensure adequate delivery.

**Objective:** To determine the number of breaths required to adequately inhale placebo through a variety of spacers/VHCs.

**Design:** This was a substudy from a clinical trial comparing 2 different spacers/VHCs.

**Participants:** 118 asthmatic children (aged 2 to 7 years) were included in this substudy.

**Methods:** Children inhaled placebo using the tidal breathing technique through 4 different spacers/VHCs: Aerochamber Plus, Funhaler, Volumatic, or modified soft drink bottle. Ten of these children also used the single maximal inhalation technique. Tidal volume and breathing pattern were recorded using a custom-built device that did not affect the spacer/VHC. The breathing patterns were analyzed digitally and then transferred to a breathing simulator. In the simulator, drug delivery (using an inspiratory filter at the end of the spacer/VHC) with different tidal volumes (single maximal inhalation and 2, 3, 5, and 9 breaths) were compared.

**Results:** In general, children using the tidal breathing technique demonstrated larger tidal volumes than expected (384 to 445 mL). For the Aerochamber Plus, the Funhaler (small volume VHCs), and the modified soft drink bottle, the mean drug delivery was no different whether 2, 3, 5, or 9 tidal breaths were used. For the Volumetric VHC, drug delivery was similar whether 3, 5, or 9 tidal breaths were used, but it was significantly less when 2 tidal breaths were used. Drug delivery was not improved for any device when a single maximal inhalation was used.

**Conclusions:** For young asthmatic children, 2 tidal breaths may be adequate to ensure acceptable drug deposition with small-volume VHCs, whereas 3 tidal breaths may be necessary for large-volume VHCs.

**Reviewer’s Comments:** This is the first study I am aware of that addresses the question of how many tidal breaths are necessary to ensure acceptable delivery of inhaled medications with a valved holding device to young children who cannot take a single maximal inhalation. Further in vivo studies looking at lung deposition with different number of tidal breaths would be valuable. (Reviewer-Oren Lakser, MD).

**Keywords:** Pediatric, Asthma, Spacers, Aerosol Inhalation

**Print Tag:** Refer to original journal article
This study remains timely because it is a departure from previous standards stating that 50% tracheal collapsibility was sufficient for the diagnosis of tracheomalacia. Also, it sets the stage for subsequent studies regarding bronchomalacia.

**Background:** Tracheomalacia is increasingly recognized as a cause of chronic cough and other respiratory symptoms. Dynamic CT has been recognized as an effective noninvasive method for diagnosing tracheomalacia, with >50% expiratory reduction in the tracheal lumen being diagnostic of the disorder. However, studies have suggested that the tracheae of normal individuals may exceed a 50% expiratory reduction in luminal cross-section, leading to an over-diagnosis of tracheomalacia.

**Objective:** To evaluate the results of CT analysis of tracheal collapsibility at forced expiration in healthy individuals, and to compare this with current diagnostic criteria for tracheomalacia.

**Design/Participants:** The institutional review board-approved and the Health Insurance Portability and Accountability Act-compliant prospective study used healthy volunteers aged 25 to 75 years. Patients had no respiratory symptoms or known disease and did not smoke. Patients were excluded for pregnancy, risk factors for tracheomalacia, and abnormal spirometry. The final study population was composed of 51 participants with ages varying throughout the recruitment range of 25 to 75 years.

**Methods:** All participants were imaged with a multi-detector CT using a low-dose technique. A certified respiratory physiologist was present to monitor and coach participants with breathing instructions. Spirometric monitoring was used to ensure image capture in full inspiration and during forced exhalation. Single images were selected at 1 cm above the aortic arch and 1 cm above the carina in inspiration and expiration; coronal and sagittal images were obtained, as was a cross-sectional area of the airway using a tool involving tracing the inner wall of the airway. Also, visual classification of the shape of the trachea was performed at a level 1 cm above the aortic arch.

**Results:** The mean percentage of expiratory reduction in the tracheal cross-sectional area was 54% in the upper trachea and 56% in the lower trachea. Using the current diagnostic criteria of >50% reduction in expiratory tracheal lumen cross-sectional area, 78% of participants met criteria for tracheomalacia in the upper and/or lower trachea. If the diagnostic criterion for tracheomalacia is raised from 50% to 70% collapsibility, the false-positive rate is reduced from 65% to 22%. In this study, correlation between expiratory tracheal shape and tracheomalacia was not pronounced.

**Conclusions:** The data suggest that the diagnostic threshold for the diagnosis of tracheomalacia should be increased from the current value of 50% collapsibility. However, data were obtained only for healthy subjects. This should be expanded to include patients with tracheomalacia, as well as other clinical factors, to derive a robust set of criteria for this diagnosis.

**Reviewer’s Comments:** This study points out the need for revised criteria for the CT diagnosis of tracheomalacia. However, it needs to be expanded before ideal sensitivity and specificity are attained. Subsequent articles now available also discuss CT assessment of bronchomalacia. This study remains timely because it is a departure from previous standards stating that 50% tracheal collapsibility was sufficient for the diagnosis of tracheomalacia. Also, it sets the stage for subsequent studies regarding bronchomalacia. (Reviewer—Steven Montner, MD).

**Keywords:** Trachea, Tracheomalacia, Normal Volunteers, Collapsibility

**Print Tag:** Refer to original journal article
Prophylactic Cranial Irradiation for NSCLC Patients Not Yet Recommended

Phase III Comparison of Prophylactic Cranial Irradiation Versus Observation in Patients with Locally Advanced Non-Small-Cell Lung Cancer: Primary Analysis of Radiation Therapy Oncology Group Study RTOG 0214.

Gore EM, Bae K, et al:

J Clin Oncol 2011; 29 (January 20): 272-278

Currently, prophylactic cranial irradiation is not beneficial in patients with non-small-cell lung cancer, and the procedure should not be performed outside of a clinical trial.

Background: Non-small-cell lung cancer (NSCLC) is an incredibly aggressive malignancy with a high rate of recurrence even in early stages. Prior studies have revealed that new metastatic brain lesions occur in 22% to 55% of patients most often in the first 6 to 12 months after diagnosis. Previous trials demonstrated no benefit with prophylactic cranial irradiation (PCI) in early stage lung cancer.

Objective: Given new techniques in radiotherapy, PCI was evaluated to attempt to improve on these past outcomes.

Methods: Patients with stage III NSCLC were treated with multimodality therapy, which might include surgery and/or radiation therapy (RT) with or without chemotherapy. Patients who were demonstrated to have no evidence of disease progression were randomized to either PCI (30 Gy in 15 fractions) or observation. Stratification was based on histology and surgical resection. The primary end point was overall survival (OS), while secondary end points were disease-free survival (DFS), neurocognitive function (NCF), and quality of life (QoL). The study was designed to test whether OS was improved by 20% at 1 year, for which 1048 patients would have been required.

Results: The trial was closed early due to slow accrual after enrollment of only 340 eligible patients. There was no statistical difference in median overall survival (25.8 vs 24.8 months; \( P = 0.86 \)) or DFS (56.4\% vs 51.2\%; \( P = 0.11 \)) at 1 year with PCI versus observation, respectively. There was, however, a significant decrease in the rate of 1-year brain metastases for those who received PCI (7.7\% vs 18.0\%; \( P = 0.004 \)). This corresponded to an odds ratio for developing brain metastases of 2.52 (ie, patients in the observation arm were 2.52 times more likely to develop brain metastases). There was no difference in QoL; however, there was a significant decrease in neurocognitive function (NCF) for those who received PCI, although this was not discussed extensively in the paper.

Conclusions: Although PCI decreased the risk of developing brain metastases, it did not lead to an improvement in OS or DFS and came at the cost of worse NCF.

Reviewer’s Comments: New brain metastases with NSCLC are not an uncommon outcome for patients with early stage disease. This comes with both increased morbidity and mortality. If one could decrease this risk and improve survival with minimal toxicity, the standard of care would likely change overnight. Unfortunately, this was a negative trial that was underpowered due to slow accrual. Brain metastasis were lower than expected in both arms (likely based on the selection of patients who had not progressed after treatment) but decreased significantly with PCI. This paper confirms earlier trials performed over the past 3 decades. Although this trial did show a decrease in brain metastasis with PCI, PCI cannot be recommended for any patients with NSCLC, and the procedure should not be performed outside of a clinical trial. (Reviewer-Victoria M. Villaflor, MD).

Keywords: Lung Cancer, Radiation, Observation

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Independent predictors of acute pulmonary embolism include age, obesity, comorbid conditions, and certain aspects of the type of pulmonary embolism risk factors.

**Background:** To date, our understanding of the consequences of acute pulmonary embolism (PE) is largely limited to analysis of mortality, complications, and recurrence.

**Objective:** To broaden our understanding by using quality of life (QoL) scores in patients after acute PE.

**Design:** Dutch, single-center, academic institution, prospective analysis on patients involved in a follow-up outcomes study on PE.

**Methods:** The authors used the Short Form 36 (SF-36) on survivors of acute PE at least 1 year out from their event. For comparison, normal values on the SF-36 from the Dutch population were used. The primary endpoints were QoL and the 9 subscales encompassed by the SF-36. In a secondary analysis, multivariate logistic regression was used to evaluate how QoL was influenced by a number of PE- and non-PE-related variables (age, sex, obesity, active malignancy, cardiopulmonary disease, central PE, and recurrent PE).

**Results:** The primary analysis revealed that, of the SF-36 subsets, mental health and health change over 1 year were preserved. The remaining 7 fields of QoL (physical functioning, social functioning, physical role limitation, emotional health limitation, vitality, bodily pain, and general health perceptions) were all significantly worse than the comparison group (Dutch norms). The greatest difference was seen in physical role limitation. In the multivariate analysis, obesity, active malignancy, and cardiopulmonary diseases were all associated with worse QoL. Notably, centrally located PE was not associated with any QoL field decrement. Increasing time from PE event was inversely associated with QoL worsening in several subscales. Of the risk factors associated with the acute PE, transient risk factors (ie, pregnancy) were associated with better QoL, whereas permanent PE risk factors (eg, malignancy) and unprovoked PE were associated with worse QoL. Based on the goodness of fit coefficient, only a minority of the QoL variation after PE is explained by factors explored in this investigation. The authors suggest that PE-specific QoL scoring systems and other demographic and psychosocial factors may improve the analysis.

**Conclusions:** A number of PE-dependent variables as well as factors unrelated to PE are associated with QoL after acute PE.

**Reviewer's Comments:** QoL is a unique outcome assessment after PE. The current analysis excluded the group of 2% to 4% of patients with PE who go on to develop pulmonary hypertension. Furthermore, the number of patients who did not respond to the questionnaire outnumbered responders. This group of nonresponders (not included in the study) had a substantially higher proportion of transient PE risk factors that seems to be associated with better QoL. Further refinement and identification of factors associated with more specific QoL measures pertinent to PE need exploration. (Reviewer-Ajeet G. Vinayak, MD).

Keywords: Quality of Life, Acute Pulmonary Embolism

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